PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32633A/DFC	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 03/04480	International filing date *(day/month/year)* 10.10.2003	Priority date *(day/month/year)* 11.10.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/427		
Applicant DANA-FARBER CANCER INSTITUTE INC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.03.2004	07.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Siatou, E Telephone No. +49 30 25901-327

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/04480

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-14 as originally filed

Claims, Numbers

1-17 filed with telefax on 14.10.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-9,15 in respect of IA

   because:

   ☒ the said international application, or the said claims Nos. 1-9,15 in respect of IA relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9, 12, 14-15
	No:	Claims	10-11, 13, 16-17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	10-14,16-17
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-9 and 15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Amended claims 1-17 can be regarded as meeting the requirements of Art. 34(2)(b) PCT.

2. Reference is made to the following documents:
D1: WO 99/02514 A
D2: US 2002/058286 A1
D3: US-B-6 399 6381
D4: WO 99/43320 A
D5: WO 01/64650 A

3. Documents **D1-D3** and **D5** , all disclose(cf. **D1** claims 1-5, page 8, lines 31-32 and page 10, line 10-page 11, line 12, **D2** page 32, paragraph 332- page 33, paragraph 335 and claims 1-35, **D3** claims 1-7, column 6, line 57- column 7, line 18 and **D5** claims 1-63, page 12, lines 4-21, page 77, line 29, page 78, lines 5-28) the use of epothilone derivatives for treating multiple myeloma, either alone or in combination with other chemotherapeutic agents. The subject matter of independent claim 1 differs from the prior art in the chemical structure of the epothilone derivatives used.
Document **D4** discloses the use of epothilones falling under formula (I) for treating a variety of cancers, from which the subject matter of claim 1 differs in that treatment of multiple myeloma is not mentioned.
Thus, independent claim 1 is new over the cited prior art (Art. 33(2) PCT).

4. The same argumentation applies mutatis mutandis to the subject matter of claims 14-15 (Art. 33(2) PCT).

5. Document **D4** discloses (cf. page 9, last paragraph- page 11, line 7, page 17, line 1-

page 18, line 6 and page 23, lines 4-11) combination products and kits containing these, comprising epothilones and known anticancer agents, such as alkylating agents, for the treatment of cancer, especially cancer that is refractory to the treatment with other chemotherapeutics. Epothilone B is specifically mentioned. Thus, the subject matter of claims 10-11, 13, 16-17 is not novel over D4 (Art. 33(2) PCT).

6. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of the present application does not involve an inventive step in the sense of Article 33(3) PCT.

The document **D2** is regarded as being the closest prior art to the subject-matter of the present application, and discloses the use of epothilone derivatives, alone or in combination with other known anticancer agents, for treating multiple myeloma.
The subject-matter of the present claims therefore differs from this known compositions in the structure of the epothilone derivatives used.
The problem to be solved by the present invention may therefore be regarded as providing further compositions for treating myeloma.
The solution proposed cannot be considered as involving an inventive step (Article 33(3) PCT) since the epothilones derivatives of formula (I) of the present application are already known in the prior art as anticancer agents, especially cancer that is refractory to the treatment with other chemotherapeutics (see **D4**).

7. Dependent claims 2-9, 12 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, see documents D1-D5 and the corresponding passages cited in the search report.

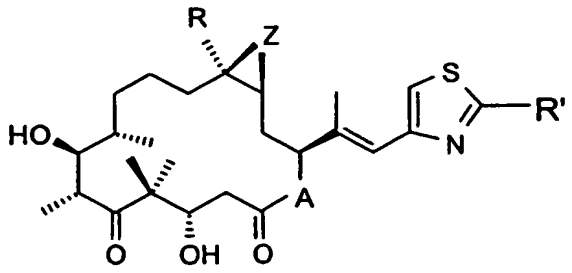
8. For the assessment of the present claims 1-9, 15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

9. The subject matter of claims 10-14, 16-17 is industrially applicable (Art. 33(4) PCT).

What is claimed

1. A method of treating a warm-blooded animal having myeloma comprising administering a therapeutically effective amount of an epothilone.

2. The method of claim 1 wherein the epothilone is a compound of formula I



(I)

wherein A represents O or NR_N, wherein R_N is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino or methylthio, and Z is O or a bond,
or a pharmaceutically acceptable salt thereof to a warm-blooded animal in need thereof.

3. The method according to claim 1 or 2 wherein the warm-blooded animal is a human.

4. A method according to anyone of claims 1 to 3 wherein the myeloma is resistant to conventional cytotoxic chemotherapy.

5. A method according to anyone of claims 1 to 3 wherein overexpression of the multi-drug resistance protein p170 is observed.

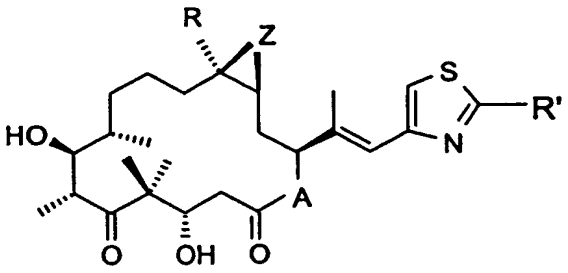
6. A method according to anyone of claims 1 to 3 wherein the myeloma is resistant to a taxane, e.g., paclitaxel.

7. The method according to anyone of claims 1 to 6 wherein the disease is multiple myeloma.

8. The method according to anyone of claims 1 to 7 wherein the compound of formula I is epothilone B.

9. The method according to 8 comprising administering epothilone B weekly in a dose that is between about 0.1 to 6 mg/m^2 for three weeks after an interval of one to six weeks after the preceding treatment.

10. A combination comprising (a) an epothilone of formula I



(I)

wherein A represents O or NR_N, wherein R_N is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino or methylthio, and Z is O or a bond, and (b) at least one compound selected from the group consisting of alkylating agents, corticosteroids and anthracyclines, in which the active ingredients (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier, for simultaneous, separate or sequential use in the treatment of myeloma.

11. Combination according to claim 10 wherein the epothilone is epothilone B.

12. Combination according to claim 11 or 12 for simultaneous, separate or sequential use in the treatment of multiple myeloma.

13. Use of a combination according to claim 11 or 12 for the preparation of a medicament for the treatment of myeloma.

14. A method of treating myeloma comprising administering a combination as defined in claim 11 in an amount which is jointly therapeutically effective against myeloma to a warm-blooded animal in need thereof.

15. A pharmaceutical composition comprising a quantity, which is jointly therapeutically effective against myeloma, of a combination according to claim 11 and at least one pharmaceutically acceptable carrier.

16. A commercial package comprising a combination as defined in claim 11, together with instructions for simultaneous, separate or sequential use thereof in the treatment of myeloma.